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Immunomodulation and immune thrombocytopenia: some unmet needs, questions, and outlook

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ABSTRACT

During the last two decades, new therapeutic strategies have been developed, particularly anti-CD20 agents and thrombopoietin-receptor (TPO-r) mimetics, for immune thrombocytopenia (ITP). However, although the new efficient drugs have deeply modified the therapeutic strategy and the disease prognosis, there are still unmet needs and challenges. Concerning rituximab, reassuring data concerning its safety have recently been reported. The main limitation of the treatment is its modest long-term efficacy, with frequent disease relapse. Maintenance treatment or association with other immunomodulatory drugs such as dexamethasone may achieve better long-term response. With failure of one of the available TPO-r agonists (ie, romiplostim and eltrombopag), another can be used. Switching may be beneficial, with more than 50% chance of response, and could limit the risk of platelet fluctuation occasionally observed with these treatments. According to the mechanism of action of TPO-r agonists, a rapid relapse of thrombocytopenia should be observed after they are stopped. Several recent observational studies suggested sustained responses in patients achieving complete response with TPO-r agonists and who stopped the treatments. Prospective studies to confirm these unexpected data are needed. Thrombosis in ITP is a concern, particularly with TPO-r agonists, even though the pivotal studies of eltrombopag and romiplostim did not report a higher incidence of thrombosis events with TPO-r agonists than placebo. Despite these reassuring data, the risk of thrombosis with TPO-r agonists remains unanswered, particularly with secondary ITP or in older adults.

Immune thrombocytopenia (ITP) is an acquired bleeding disorder characterized by antibody-mediated destruction of platelets and impaired thrombopoiesis. ITP treatment has long been based on only splenectomy and the use of cortiosteroids.

During the last two decades, new therapeutic strategies have been developed, particularly anti-CD20 agents and thrombopoietin-receptor (TPO-r) mimetics. This revolution has been possible with better knowledge of the pathophysiology of ITP and particularly the description of impaired platelet production in ITP. However, although the emergence of new efficient drugs has deeply modified the therapeutic strategy and the disease prognosis, there are still unmet needs and challenges.

This article focuses on these issues and outlooks for the treatment of ITP.

1. Rituximab in ITP: pros and cons and perspectives

Rituximab (RTX) was first used to treat lymphoma, but its use for various autoimmune diseases seemed logical, considering the important role of B cells in autoimmunity [1]. Studies reporting the efficacy of RTX for ITP were published more than 10 years ago [2,3]. Two meta-analyses confirmed the good short-term efficacy of RTX in splenectomized and non-splenectomized patients [4,5]. Thus, in most countries, RTX is used before splenectomy. For example, in France, more than 3,000 adults are admitted to hospital each year for ITP; almost 700 receive RTX, which could explain the decrease in frequency of splenectomy [6,7].

One crucial question of the use of RTX for ITP is its safety. Exceptional cases of fatal infection with JC virus after treatment with rituximab have been reported [8]. Data from a prospective French cohort of almost 250 adults receiving RTX for ITP were reassuring. The incidence of severe infection appeared rare, with only 11 episodes in seven patients without severe opportunistic infection [9]. Only three deaths due to infection occurred in three patients older than 70 years. The role of RTX in these fatal infections is questionable.

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The short-term efficacy of RTX is good. However, B-cell depletion induced by RTX infusions is always transient, with a complete B-cell repopulation after 6–12 months. This fact could explain the modest long-term response; in a retrospective study [10], the proportion of long-term responders was about 20% in adults and 25% in children. These modest results were confirmed by two recent prospective studies. In the French prospective cohort cited previously, the median time to relapse for patients who initially responded to rituximab was 24 months. A randomized double-blind study comparing rituximab and placebo in ITP [11] did not find a reduction in rate of long-term treatment failure with RTX treatment. How to obtain better long-term results remains an important question.

One way to avoid useless treatment with RTX would be to better select patients. Unfortunately, strong predictive factors of response are lacking. Another option could be to administer maintenance treatment to avoid relapse as for other diseases such as rheumatoid arthritis (RA) [12], ANCA-associated vasculitis [13], or malignant lymphoma [14]. However, we have no firm data on maintenance treatment with RTX in ITP. The study by Jim Bussel's group showed that new infusions of RTX gave the same results as the first infusion in more than 70% of cases [15]. In this setting, the risk of infection and hypogammaglobulinemia is a concern.

The experience of rheumatologists is reassuring. The long-term safety of RTX was assessed in a large register including more than 3,000 patients with RA treated with up to 17 courses of RTX; more than 800 patients received at least six treatment courses [12]. In most patients, RTX was associated with methotrexate. The incidence of serious infection was only 3.96/100 patient-years and was similar to that observed with methotrexate alone. The authors concluded no evidence of increased safety risk or increased reporting of any types of adverse events with prolonged exposure to RTX during the 9.5 years of observation. Acceptable safety of maintenance treatment with rituximab was also reported in patients with ANCA-associated vasculitis [13]. Despite these reassuring results, prospective studies of ITP should be conducted to ensure the safety of this strategy in this disease.

RTX could be associated with another treatment. Two recent studies highly suggested that the association of RTX with dexamethasone and other immunosuppressive drugs could achieve longer response. Bussel and colleagues [16] reported that after several oral courses of dexamethasone combined with RTX infusion, the estimated 5-year response rate was 44% but was previously reported as only 20% with RTX alone in adults [10,17]. A recent prospective open study including only 20 patients receiving low doses of RTX (only 4 weekly infusions of 100 mg) with a short course of dexamethasone and cyclosporine gave promising results, with a free relapse event rate of 76% after 24 months of follow-up. However, the risk of hypogammaglobulinemia in this setting should be emphasized [16,18].

2. TPO-r agonists and ITP: pros and cons and perspectives

TPO-r agonists entered clinical trials more than 10 years ago. Within 5 years of their licensure, they have revolutionized the treatment of ITP. Their efficacy has been clearly demonstrated in robust prospective randomized studies, with response in about 70% of patients and with good short-term safety [19]. Questions remain about the long-term safety and the potential risk of reticulin deposits in bone marrow. Prospective studies are being conducted to answer this important question [20].

Several studies [21–23] demonstrated that with failure of one of the available TPO-r agonists (ie, romiplostim and eltrombopag), the other could be used. Switching may be beneficial, with more than 50% chance of response. We have no firm explanation for this pattern of response. Strong differences exist between romiplostim, a peptibody, and eltrombopag, a small molecule that binds to different sites on the TPO-r. In view of these results, it would make sense to switch from one TPO-r agonist to the other with lack of response or with adverse effects. Of concern in the use of TPO-r agonists for both physicians and patients is the occurrence of unexpected marked platelet-count fluctuations, which sometimes necessitate rescue therapy and/or a reduction, transient withdrawal or increase in TPO-r agonist dose. In this case, switching can be useful and can lead to a more stable platelet count [21].

According to the mechanism of action of TPO-r agonists, a rapid relapse of thrombocytopenia should be observed after they are stopped. In theory, TPO-r agonist treatment should be maintained with response. Unexpectedly, several retrospective recent observational studies suggested a sustained response in patients showing complete response with TPO-r agonists and who stopped the treatment [24–27]. The mechanisms by which TPO-r agonists may induce durable remission are far from being understood. The agents could restore the number and function of T-regulatory lymphocytes [28]. Prospective studies to confirm the unexpected data are required, but in clinical practice, progressive discontinuation of TPO-r agonists in patients showing prolonged complete response could be tried.

The mechanisms of failure of TPO-r agonists are not well known. One study [29] showed that eltrombopag could stimulate megacaryocyte proliferation and maturation but had no effect on the final steps of platelet production and release. Comparison of responders and non-responders to eltrombopag demonstrated an increased number of megacaryocytes in bone marrow of both responders and non-responders, but non-responders showed no platelet formation and release. Absence of platelet release could be due to platelet antibodies, and adding azathioprine allowed one patient to achieve response. From a clinical perspective, a strategy to overcome resistance to TPO-r agonists may involve adding conventional immunosuppressive agents to inhibit autoantibody production [30].

3. Is ITP a risk factor of thrombosis?

Thrombosis in ITP is a concern, particularly with the use of TPO-r agonists, even though the pivotal studies conducted with eltrombopag and romiplostim did not report a higher incidence of thrombosis events with TPO-r agonist treatment as compared with placebo [31,32]. Several recent studies based on administrative databases suggested that ITP could be paradoxically associated with a higher risk of thrombosis than in the general population [33–36]. However, these studies did not evaluate personal and treatment-related risk factors. A recent retrospective multicenter investigation was of a large cohort of patients requiring at least one treatment for ITP recruited from major tertiary Italian centers treating ITP [37]. Data for 986 patients were analyzed. As compared with data reported in previous studies, the 5-year cumulative incidence of venous and arterial thrombosis in ITP was well below the predefined thresholds, and venous and arterial thromboembolism were not frequent complications in ITP, except in particular settings, such as in splenectomized and older patients. Despite these reassuring data, the risk of thrombosis associated with TPO-r agonists remains an unanswered question, because only a few patients included in the study received TPO-mimetics. A recent study suggested that romiplostim could be associated with increased risk of thrombosis events in older adults [38]. An analysis of the WHO global individual case safety report database (VigiBase) found an increased risk of thrombosis with eltrombopag compared with romiplostim [39]. These results must be confirmed and quantified by large etiological pharmacoepidemiological studies.